ABSTRACT

A small percentage of cells within an established solid tumor have the properties of stem cells. These solid tumor stem cells give rise both to more tumor stem cells and to the majority of cells in the tumor that have lost the capacity for extensive proliferation and the ability to give rise to new tumors. Thus, solid tumor heterogeneity reflects the presence of tumor cell progeny arising from a solid tumor stem cell. This discovery is the basis for solid tumor stem cell compositions, methods for distinguishing functionally different populations of tumor cells, methods for using these tumor cell populations for studying the effects of therapeutic agents on tumor growth, and methods for identifying and testing novel anti-cancer therapies directed to solid tumor stem cells.

We have developed a xenograft model in which we have been able to establish tumors from primary tumors via injection of tumors in the mammary gland of severely immunodeficient mice. Xenograft tumors have been established from mastectomy specimens of breast cancer patients. Furthermore, in the three tumors that we have tested, we have been able to make single-cell suspensions and transfer the tumors serially through immunocompromised mice. These improvements in the xenograft assay have allowed us to do biological and molecular assays to characterize clonogenic solid tumor stem cells.

We have also developed evidence that strongly implicates the Notch pathway, especially Notch 4, as playing a central pathway in carcinogenesis. Antibodies against Notch4 reduced tumor cell proliferation and survival.